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EXAMINER
LUCAS, ZACHARIAH

ART UNIT	PAPER NUMBER
1648	#26

DATE MAILED: 06/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/368,076	JIN ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36-44* is/are pending in the application.

4a) Of the above claim(s) *36-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *21* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of the Application

1. Claims 36-44 are pending in the application. Claims 36-39 stand withdrawn as to non-elected inventions. Claims 40-44 are under consideration.

2. Claims 40-43 were rejected in the Final Action mailed on October 22, 2002 (the prior action). The Applicant filed a Request for Continued Examination (the RCE) on March 24, 2003. In the RCE, Applicant amended claims 37, 39, 40,41, and 43, and added new claim 44.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on March 24, 2003 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

Specification

4. **(Prior Objection- Withdrawn)** The disclosure was objected to in the prior action because of the following informalities: the application incorrectly identified the set of primers used to create the claimed substitutions. In view of the amendment of the specification, the objection is withdrawn.

Claim Objections

5. **(Prior Objection-Withdrawn)** Claim 43 was objected to in the prior action because of the following informalities: the claim improperly uses the word "or" rather than "and" between

the last two members of the Markush Group. In view of the Amendments to this claim, the objection is withdrawn.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. **(Prior Rejection- Maintained)** Claims 40 and 41 were rejected in the prior action under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated infectious RSV comprising a substitution of a glycine for cysteine residue 96, does not reasonably provide enablement for an isolated RSV wherein any cysteine residue has been substituted. The Applicant traverses this rejection in the grounds that the application enables one skilled in the art to make, and that the Examiner has provided no evidence as to the non-operability of, the claimed inventions, wherein the identified cysteines are substituted with a glycine, valine, aspartic acid, or alanine. The Examiner did not, and does not contest the ability of those in the art to make these mutated RSV. Thus, the Applicant's arguments on these grounds are moot. The second argument in traversal, that the Examiner has not provided adequate evidence of non-operability of the claimed invention, is not found persuasive.

The Applicant argues that because neither Hardy, nor Collins, specifically identifies the claimed substitutions as non-operable, they are not relevant evidence against the claimed invention. Although the Examiner agrees that the references do not teach that the claimed substitutions specifically are in operable, the Examiner does not agree with the Applicant's

assessment of the teachings. These references teach that the zinc-binding motif of the M2-1 protein is necessary to the protein's function. See, Hardy, page 5884, and U.S. Patent 6,376,171, column 2, lines 31-45 (teaching that conservation of the Cys_3-His motif is required for protein function, and not that only serine substitutions destroy that functionality). The claimed mutations destroy that motif. Furthermore, teachings in the art indicate that the M2-1 protein is "is a necessary component of functional nucleocapsids during productive infection." See, U.S. Patent 5,993,824, column 31, lines 15-39. Thus, the art teaches that some functionality of this protein is required in order for the recombinant RSV to be an effective live vaccine, but that the destruction of the zinc-binding motif also destroys the ability of the protein to function. The Examiner has therefore provided evidence that the claimed embodiments wherein members of the motif are substituted render the recombinant RSV inoperable.

Furthermore, while the Examiner has provided evidence in support of the rejection, Applicant has nowhere provided any working examples or other evidence to show that the presently claimed mutations do not destroy the function of the M2-1 protein. Rather, while the Applicant was able to successfully isolate recombinant RSV from cells transfected with plasmids encoding for the Cysteine substitution at position 96, the application indicates, by exclusion, that no RSV particles were isolated from cells transfected with plasmids encoding the other cysteine mutants. Application, page 90. Thus, the Applicant's own teachings tend to indicate that substitutions at these positions may not result in viable attenuated RSV strains.

It is further noted that the Applicant has not fully distinguished from the substitutions made in Hardy. While Hardy does refer to serine substitutions, the teachings of Hardy refer to mutations in the zinc-binding motif generally. Among the four residues included in the list of

claim 40, one of them, glycine, is a conservative amino residue with serine, the residues used in Hardy. Along with the lack of evidence that any substitution to the zinc-binding motif would allow for any operation of the M2-1 protein, in view of the similar properties of the serine and claimed glycine substitutions, the Applicant has not provided any evidence that the particular amino residues listed in the claims would not yield similar results to the serine substitution.

Therefore, the Examiner has provided evidence that the claimed invention would not be operative. The Applicant, however, has provided no evidence to the contrary. In view of that lack of counter evidence, and of the discussion above, the rejection is maintained.

8. **(Prior Rejection- Withdrawn)** Claim 43 was rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claim was rejected for misidentifying a coding sequence. In view of the corrections to the claims, the rejection is withdrawn.

9. **(Prior Rejection-Maintained)** Claims 42 and 43 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a deletion mutant of M2-1 wherein the truncation is at amino residues 178 or 179 (nucleic acids 8137-8139 or 8140-8142 respectively), does not reasonably provide enablement for any viable truncated M2-1 protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. The Applicant traverses this traversal on the grounds that they have disclosed how to

make the claimed truncations. The Examiner would like to point out that in order to be enabled for a claimed invention, the Applicant must teach both how to make and use the claimed invention. In this case, the Examiner is not questioning the teachings of the application to the extent that they cover the making of the C-terminally truncated M2-1 proteins. Furthermore, if the Applicant had descriptive support to a C-terminal truncation of the protein generally, the Examiner would similarly have felt that the determination of which truncations would and would not be operable would have been within the capacity of those skilled in the art to determine.

However, the Applicant is claiming a series of specific truncations. In support of all of the truncations, they have shown only that the least of them (i.e. those with the smallest number of C-terminal residues removed) results in an active M2-1 protein. Application, page 92. There are no teachings in the application that would indicate to those in the art whether or not the remaining truncated proteins would be operable, or why the Applicant chose the particular truncations identified. Further, in the application, the Applicant has indicated that they themselves do not know what the effects of the further truncations will be. See, page 92 (teaching the making and decrease in activity of the truncations at residues 178 and 179, but stating that "rescue of recombinant RSV containing longer deletions in the C-terminus of the M2-1 protein is also being pursued." The Applicant has thereby demonstrated that they have not made more extensive truncations, much less determined if those identified would result in operative M2-1 proteins). Because the Applicant has not demonstrated the specifically claimed inventions are likely to result in operable inventions, and because the art, as indicated above and in the prior action, teach that an active M2-1 protein is required for RSV replication and therefore also required for a viable attenuated virus, the Applicant is not enabled for the C-

terminal truncations other than those representing truncations at amino residues 178 and 179 of the protein.

10. **(Prior Rejection-Withdrawn)** Claims 40 and 41 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims read on substitutions in the M2-1 gene wherein the substitutions result in the substitution of a glycine, valine, aspartic acid, or alanine for a native cysteine residue. In view of the support for cysteine scanning mutagenesis employing the substitution of residues other than glycine for cysteine on pages 24 and 25 of the Application, as indicated by the Applicant, the rejection is withdrawn.

11. **(New Rejection)** Claim 44 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This claim reads on an isolated infectious respiratory syncytial virus particle containing at least one M2-1 gene mutation wherein at least one mutation encodes an amino acid exchange from a cysteine to another amino acid, and wherein the cysteine residues at positions 7, 15, and 21 are retained. The rejection is on two grounds.

First, the Applicant is not enabled for the claimed invention because the claim reads on embodiments wherein the Histidine at position 25 of the protein is also mutated. As indicated

above, the art teaches that a Cys_3-His zinc-binding motif is required for M2-1 protein function. While the Applicant has excluded substitutions at the three cysteines in the present claim, because the claim permits other mutations than cysteine substitutions, the claim includes embodiments wherein the His member of the required motif has been substituted or otherwise mutated. The Applicant is not enabled for such embodiments.

Second, the Applicant is not enabled to claims to an RSV with any mutation in the M2-1 gene. As indicated above, the M2-1 gene is essential to the RSV particle's operation. However, as also described above, the Applicant has not provided any guidance as to all the potential mutations that may be performed with the gene, and still maintain the functionality of the M2-1 protein to some extent. While the application does describe a limited number of mutations that could be used, the application does not provide sufficient description of the parts of the protein necessary for its function such that one skilled in the art would be able to make and use RSV particle comprising any mutation without undue experimentation. Aside from the mutations identified above as enabled, the Applicant has not provided guidance that would lead one in the art to other mutations that would result in a mutated but viable RSV particle.

12. **(New Rejection)** Claim 44 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This claim reads on isolated attenuated RSV with "at least one M2-1 mutation, wherein at least one gene mutation encodes an amino exchange from a cysteine to an

amino acid selected from the groups comprising glycine, valine, aspartic acid, and alanine at amino acid position 96..." Because this claim reads on at least one gene mutation, and then specifies that at least one of the mutations is the cysteine substitution at position 96, and then excludes the remaining potential cysteine substitutions, the claim implicitly reads on M2-1 genes with mutations other than those disclosed in the specification.

Prior to the addition of this claim, the claimed mutations to the M2-1 protein were limited to cysteine substitutions and C-terminal truncations. Each of the independent claims 40 and 42 specifically identified the types of mutations that could be used to make the claimed RSV particle. Furthermore, the specification on page 88 of the Application presents only those two forms of mutation strategies for the making of RSV attenuated by M2-1 mutations. Thus, it would appear from the originally filed claims and from the specification describing M2-1 mutations that the Applicant was not in possession of, and had not contemplated, mutation strategies other than the two described above for the attenuation of RSV through M2-1 mutation. The Applicant therefore does not have written description support for any other potential mutations types, which would be included in the presently rejected claim. The claim is therefore rejected as containing New Matter to the application.

This claim is also rejected as containing new matter because it allows for the substitution of the cysteine at position 96 with amino acids other than the four disclosed in the claim. The application teaches cysteine-scanning mutagenesis wherein the cysteines of the M2-1 protein are substituted for one of the amino acids glycine, valine, aspartic acid, and alanine. However, the application does not teach the substitution of cysteines for other amino acids. Because the

present claim language allows for the substitution of the cysteine at position 96 with amino residues other than the 4 identified, the claim introduces New Matter to the application.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. **(New Rejection)** Claim 44 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim reads on an RSV with a cysteine substitution at residue 96, wherein the cysteine is substituted for "an amino acid selected from a group comprising glycine, valine, aspartic acid, and alanine..." It is unclear from the claim what amino residues are included in the group because the Applicant has used the open term "comprising" to identify the members. The use of this term indicates that other, undisclosed, amino acids may also be substituted for the cysteine. It is suggested that the term "comprising" be replaced with the term --consisting of--.

The claim is also indefinite for the claim language "wherein (i) at least one M2-1 gene encodes an amino acid exchange from a cysteine to an amino acid selected from... at amino acid position 96" It is unclear how there can me more than one (implied by "at least one" substitution for the same amino residue.

Claim Rejections - 35 USC § 103

(Prior Rejection-Withdrawn) Claims 40 and 41 were rejected under 35 U.S.C. 103(a) as being unpatentable over Worthington et al., supra, in view of Howorka et al. these claims read on RSV M2-1 proteins wherein the cysteine amino acids have been substituted with other amino acids. This rejection is withdrawn in view of the Applicant's argument in traversal, which was persuasive.

Conclusion

15. No Claims are allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 703-308-4240. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Z. Lucas
Patent Examiner
June 10, 2003

JAMES HOUSEL 6/16/03
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